Meeting of the
Pharmacy and Therapeutics Committee
October 31, 2005
Minutes

Members Present:
Randy Axelrod, M.D., Chair
Mark Szalwinski, R. Ph., Vice Chair
Avtar Dhillon, M.D.
James Reinhard, M.D.
Gill Abernathy, M.S., R.Ph.
Renita Warren, Pharm.D.
Mark Oley, R.Ph.
Mariann Johnson, M.D.
Roy Beveridge, M.D.
Rachel M. Selby-Penczak, M.D.

Absent:
Sue Cantrell, M.D.
Arthur Garson, M.D.

A quorum was present

Guests:
80 representatives from pharmaceutical companies, providers, advocates, associations, etc.

DMAS Staff:
Jane Woods, Secretary of Health and Human Resources
Patrick Finnerty, Agency Director
Cynthia B. Jones, Chief Deputy Director
Cheryl Roberts, Deputy Director of Programs and Operations
Bryan Tomlinson, Director, Division of Health Care Services
Reatha Kay, Counsel to the Board, Office of the Attorney General
Kevin Payne R.Ph, Pharmacy Manager
Rachel Cain, Pharm.D, Clinical Pharmacist
Keith Hayashi, R.Ph., Clinical Pharmacist
Katina Goodwyn, Pharmacy Contract Manager

First Health Staff:
David Adams, Pharm.D, Rebate Support
Debbie Moody, R.Ph, Clinical Manager
Donna Johnson, R.Ph, Clinical Manager
Doug Brown, R.Ph, Rebate Support
Justin Lester, Pharm.D, M.B.A., Rebate Support

WELCOME AND INTRODUCTIONS FROM PATRICK FINNERTY, DMAS DIRECTOR

Mr. Finnerty welcomed everyone and expressed his appreciation for their attendance. He noted the full agenda and reviewed the topics to be discussed which included: the quarterly review of new drugs in PDL eligible drug classes, an annual review of the Phase I drug classes (14), and the evaluation of financial information for six potential new drug classes. Mr. Finnerty stated that at the last meeting, the Committee received great presentations from the DMAS staff, First Health Services Corporation and Dr. Randy Axelrod on various topics. Dr. Axelrod presented information on specialty drug management; the DMAS and First Health staff spoke about impending changes related to the implementation of Medicare Part D; and DMAS' Policy and Research staff presented financial and health impact analyses of the PDL program. All of those reports are publicly available on the DMAS website.

Following the meeting, the Department will release a *Medicaid Memo* to medical and pharmacy providers regarding the PDL changes discussed, which will be implemented in January 2006. This information will also be available on the DMAS web site. The memo will include information for pharmacy providers regarding changes due to the implementation of Medicare Part D. The Department continues to work along with its partners for the smooth transition of dual eligible recipients to Medicare Part D. Mr. Finnerty noted that Virginia Medicaid would continue to provide coverage of some pharmaceuticals that are not covered under part D, but for which the state Medicaid program can continue to receive federal financial participation. This includes over the counter medications, barbiturates, benzodiazepines, some vitamins and mineral products and other drugs specifically excluded from Part D coverage. The Department will continue to update the P&T Committee as Medicare Part D is implemented.

COMMENTS AND WELCOME FROM JANE WOODS, SECRETARY OF HEALTH AND HUMAN RESOURCES

Secretary Woods expressed her gratitude for the Committee's attendance. She stated that the Administration appreciated the Committee's work throughout the PDL process. The program's success would not have been possible without the expertise and commitment of time shared so readily by the Committee. As a token of the Administration's gratitude, Secretary Woods presented each member of

the Committee with a letter of appreciation from the Governor and a Commonwealth of Virginia lapel pin.

Secretary Woods welcomed Dr. Rachel Selby- Penczak to her first meeting as the newest P&T Committee member. Dr. Selby- Penczak is an Assistant Professor of Medicine at the MCV Hospital (Virginia Commonwealth University Health System) and the former Medical Director at Beth Shalom nursing home. Secretary Woods noted her appreciation for the knowledge, expertise, energy and perspective Dr. Selby- Penczak brings to the Committee. She reiterated her thanks to Dr. Peter Boling at VCUHS for nominating Dr. Selby- Penczak to the Committee. Secretary Woods asked that everyone keep former member, Dr. Christine Tully, in their thoughts and prayers during her illness. She stated that Dr. Tully is missed and has been invaluable to the Committee.

Secretary Woods stated that the goal of the PDL and all Virginia Medicaid programs is to provide the best medical care without compromising the health status of recipients. With the implementation of Medicare Part D and any other extraneous forces, the Department will continue its commitment to be responsible to Virginia's taxpayers and providers.

Finally, as follow up to comments at the last meeting, Secretary Woods stated that she, along with the expertise of DMAS staff, is making recommendations to the Governor concerning drugs for the treatment of erectile dysfunction (ED). There has been a lot of discussion on the topic and a decision brief will be forwarded to the Governor for review and decision within a week. Congress has passed legislation that as of January 1, 2006 federal funding to Medicaid program will be terminated for ED drugs. Virginia and other states will now have sole financial responsibility for the coverage of these drugs, if continued. The decision will not effect the Governor's prior action of discontinuing ED drug coverage for Virginia Medicaid recipients who are registered sex offenders.

Secretary Woods thanked the Committee again on the behalf of the Administration for their extraordinary efforts that made the PDL program an unbelievable success.

COMMENTS AND WELCOME FROM DR. RANDY AXELROD, CHAIRMAN

Dr. Axelrod also welcomed Dr. Selby- Penczak to the P&T Committee. He stated that she will be able to assist the Committee through its difficult issues and noted his appreciation for her commitment of time and efforts. Dr. Axelrod noted the previous presentation of the PDL analyses by Wayne Turnage (DMAS) and the tremendous information provided on the program's success. The report reflected good cost containment, appropriate care, and no changes in patient access (or a sentinel effect of potential lack of access). All of those accomplishments were attributed to the P&T Committee as well as all of the information provided by pharmaceutical industry and clinical consultants from around Virginia. Dr. Axelrod thanked the Committee for over two years of work.

On behalf of the Committee, Dr. Axelrod expressed his appreciation to the Governor, Secretary Woods, Mr. Finnerty, and the entire DMAS team for the past two and a half years of effort. Dr. Axelrod presented a plaque to Secretary Woods, from the P&T Committee and the Department, to show appreciation for her leadership in tackling some of the tough pharmacy program and political issues. Dr. Axelrod stated that Secretary Woods helped steer the course, particularly with her selection of members for the successful P&T Committee. He noted that Secretary Woods' participation in the meetings helped to bring a clear focal point to the Committee along with the collaboration of private and public sector representatives for the betterment of all Virginians.

Dr. Axelrod reiterated that there was a full agenda. He reminded the presenters of the three minute time limit being monitored by a time clock. In addition, he noted that it was the third review of Phase I PDL drug classes and only information that is new since the last presentation should be discussed to ensure that the meeting was as efficient as possible

ACCEPTANCE OF MINUTES FROM JUNE 8, 2005 AND AUGUST 31, 2005 MEETINGS

Dr. Axelrod asked if there were any corrections, additions or deletions to the minutes from the June 8, 2005 and August 31, 2005 meetings. None were noted and upon request of the Chairman, the Committee voted on a motion and a second to approve the minutes of the June 8, 2005 and August 31, 2005 meetings as written. The Committee voted unanimously to approve both sets of the minutes as drafted.

REVIEW OF NEW DRUGS IN EXISTING PDL CLASSES

Dr. Axelrod noted that there are no presenters for new drugs in current PDL classes. He asked Mr. Szalwinski to review the new dugs for the Committee.

Mark Szalwinski reviewed Quinolones and the new drug Factive®

Gemifloxacin, brand name Factive®, is a Quinolone manufactured by Oscient. It is available in a 320mg tablet. Usual dosing is: oral adult dose, 320mg daily for 5 to 14 days, depending on the organism and site of infection. Its indications are for Lower Respiratory Tract infections and community-acquired pneumonia. There is no advantage or disadvantage seen when compared to other Quinolones.

Dr. Axelrod asked if there were any questions from the Committee. With no questions from the Committee, Dr. Axelrod asked Mr. Szalwinski to continue.

Mark Szalwinski reviewed Macrolides and the new drugs Biaxin® and Zmax™

Two new Macrolides formulations were reviewed: the first one is the generic of Biaxin®, Clarithromycin, and the second is a once a day Azithromycin marketed as Zmax™.

The Clarithromycin generic is comparable to the brand Biaxin® with the same dosing, side effects and efficacy profile as the brand. It is made by various generic manufacturers. ZMAX® was released by Pfizer on June 10, 2005 and is an extended release formulation utilizing microsphere technology, which provides for a complete course of therapy in a single two-gram dose. In the first 24 hours after a dose of Zmax®, the amount of drug released into the tissue is three times higher than a standard dose of immediate-release azithromycin. ZMAX® currently has two indications of acute bacterial sinusitis (ABS) and community acquired pneumonia (CAP). ZMAX® does not have pediatric indications.

The possible side effects/ potential contraindications are the same for the entire Macrolides class, which include gastrointestinal effects, prolonged QT interval, and possible hepatic dysfunction.

Mark Szalwinski reviewed Bisphosphonates and the new drug Actonel® with Calcium CO-PACK

Actonel® with Calcium CO-PACK is a Bisphosphonate with the generic name of Risedronate/ calcium carbonate. This product is packaged in combination with calcium carbonate for the prevention and treatment of postmenopausal osteoporosis. The two products are now packaged to include four weeks of therapy. It is supplied in a 28-day course blister package containing 4 risedronate and 24 calcium carbonate tablets. Actonel® with Calcium CO-PACK is made by Procter & Gamble with OSG Norwich and co-marketed with Aventis. It has two indications: Prevention of osteoporosis in post-menopausal women and treatment of osteoporosis in post-menopausal women. Side effect profile and efficacy are class effects, which are no different for this product.

Mark Szalwinski stated that he concludes his remarks regarding new drugs.

Dr. Axelrod asked if there were any questions for Mark Szalwinski.

Dr. Axelrod noted that all three of the drug classes have been deemed as PDL eligible in the past and he asked for a nomination concerning the PDL eligibility of the four new drugs.

Mark Szalwinski motioned to make the four new drugs in the three classes (Quinolone, Macrolides and Bisphosphonates) PDL eligible.

This motion was seconded and unanimously approved by the Committee.

Phase I PDL Annual Review

HMG CoA Reductase Inhibitors (Statins)

James M McKenney, Pharm.D. President and CEO of the National Clinical Research discussed Statins

Dr. McKenney addressed the Committee and he noted that he was a lifetime citizen of the Commonwealth, who had the privilege of being a member of the National Cholesterol Education Program (NCEP) since its inception in 1985. He has served on the last two Adult Treatment Panels (II AND III), which has developed and written cholesterol treatment guidelines. These guidelines serve as a standard of care in the nation. He briefly discussed the most recent update to these guidelines and its ramifications. He noted that all the evidence accumulated over the past two decades show that there is a real relationship between cholesterol and coronary heart disease. Dr. McKenney reviewed the recommendations with the Committee. The first recommendation is that an LDL goal of less than 70 in high risk patients should be obtained. His experience is that Cardiologists are enthusiastically following this new guideline for their coronary patients. Second, an LDL goal of less than 100 should be achieved with some primary prevention patients. Finally and most importantly, he noted that if a commitment is being made to cholesterol lowering, at least a 30 to 40% reduction in LDL reduction should be accomplished. He noted that research is now suggesting that the more the LDL is lowered, the better outcome for the patient. He closed noting that in the very high risk population of diabetic patients, two new studies -- The Heart Protection study and the collaborative diabetes study -- support the new guidelines. The same trend is seen in each study; the more significant the LDL is lowered by a product, the more significant the event reduction. From these analyses, he concluded that it is very clear that the lower the LDL, the better it is for a Virginia's Medicaid population.

Dr. Axelrod asked if anyone had any questions. There were none.

Margaret Savage, MD, MPH, Medical Science Specialist from Merck/Schering-Plough Pharmaceuticals discussed the Statin, Vytorin®

Ms. Savage commented that the previous speaker noted that cholesterol levels correlate with coronary heart disease and LDL cholesterol levels correlate with heart disease events. With the new goals, more patients are eligible for aggressive therapy in addition to the lower goals. Ms. Savage stated that there are problems getting patients to goal and existing therapies have limitations. This includes the statins where most of the LDL reduction occurs. Her belief is that most clinicians do not titrate to achieve the maximum goals. Her recommendation is to move people to the new goals by the use of Vytorin®, a combination product of two agents. The two agents are a statin, simvastatin, and a second drug, esetimibe, a cholesterol absorption product. The net result of this type of dual inhibition is a deeper reduction of the LDL cholesterol levels and currently the only drug that offers this approach. With respect to clinical efficacy, Vytorin® has shown strong clinical differences in four recent head to head trials. Vytorin® reduced LDL levels by 52% at the starting dose compared to only 34% of esetimibe. Vytorin® was also able to get 83% of high risk patients to the LDL goals vs. only 46% with esetimibe alone. In head to head trials with atorvastatin, Vytorin® was superior at the equivalent dose. Ms. Savage referred to the Vytorin® PI for its excellent safety record. Ms. Savage stated that more aggressive therapy is needed for more patients because it is the only drug that uses a dual and efficient approach. It is clinically superior to its competition in four trials. It does have outcomes data and finally, it is an agent that works successfully to get patients to lower goals quickly and efficiently. These results are

particularly valuable in the Medicare population where patients are frequently disadvantaged, hard to treat, and where patient and provider compliance is key for good quality care.

Dr. Axelrod asked if anyone had any questions.

Dr. Axelrod noted that he hopes doctors titrate, not just the cholesterol treatment but blood pressure and all the other treatments.

Ms. Savage replied that if you review the outcome analysis people are not getting to goal.

Mark Henderson, PhD, Medical Information Scientist from AstraZeneca discussed the Statin, Crestor®

Dr. Henderson presented a review of two recent studies on type 2 diabetes. He mentioned that Lipitor recently received an indication for lipoprotein changes addressed in the studies being presented. The first study, the CORAL study, was a 24-week open label, randomized, parallel group, 3d multi-center study with a total of 263 type 2 diabetes patients treated with either oral agents or insulin. He described the other parameters in the study. He concluded that the primary outcome was a greater reduction in LDL with Crestor® verses Lipitor at the end of the study. The Triglycerides levels were similar between the two groups and both treatment groups were well tolerated.

The second study of type 2 diabetes was called the URANUS study. The results of this study showed that 94% of the Crestor® group vs. 88% of the Lipitor group reached their goals in 16 weeks. Similar to other clinical trials (over 12,400 patients) these studies point out the efficacy of Crestor®. These are just two of a number studies available regarding patients with high risk metabolic syndrome. Crestor® like other statins should be administered to women of childbearing ages only if they are unlikely to conceive and have been informed of the potential hazards.

Dr. Axelrod asked if anyone had any questions. There were none.

MARK SZALWINSKI REVIEWED HMG COA REDUCTASE INHIBITORS (STATINS)

In March of 2005, AstraZeneca Pharmaceuticals revised Crestor®'s package insert. The revised labeling re-emphasized recommendations made in the original label about the need for physicians to consider using lower starting doses of the drug in some individuals. Lowering of the initial dose may be particularly important for treating Asian American patients, since clinical trial data suggest that they (along with patients on cyclosporine or patients with severe renal insufficiency) may have higher drug levels and therefore, be at greater risk for muscle injury due to Crestor® than the general population. There have been a number of trials and published articles on this class in the last year. A study released in the Journal of the American Heart Association (June 2005) by researchers from Tufts-New England Medical Center's Molecular Cardiology Research Center and the Division of Cardiology compared the safety profiles of the three most commonly used statins: atorvastatin (Lipitor®), simvastatin (Zocor®), and Pravastatin (Pravachol®), versus the more recently introduced statin, rosuvastatin (Crestor®). The researchers analyzed 145 rosuvastatin-associated adverse events reported to the US Food and Drug Administration over its first year of marketing and compared the rates of such events with other statins (Lipitor®, Zocor® and Pravastatin®) simultaneously and during the respective first year of marketing. After reviewing a national database for adverse event reports, the study found rosuvastatin (Crestor®) to have the poorest safety profile. The review found that with either comparison, rosuvastatin (Crestor®) was significantly more likely to be associated with rhabdomyolysis, proteinuria, and nephropathy or kidney failure.

All have FDA indications for primary hypercholesterolemia and mixed dyslipidemia. Although not all statins have FDA indication for hypertriglyceridemia, primary dysbetalipoproteinemia (III), and homozygous familial hypercholesterolemia, these are considered class effects.

Zocor® is scheduled to go generic in the second quarter of 2006.

Mark Szalwinski motioned to keep the statin class PDL eligible. This motion was seconded and unanimously approved by the Committee.

COX-2 Inhibitors

Daniel Montero, MD, from Volvo Medical Associates discussed Cox-2 Inhibitors

Dr. Montero thanked the Committee for allowing him to speak again this year. He noted that everyone has read the same reports and have the same concerns about Cox-2 Inhibitors, which is why he wanted to address the Committee. Last year he spoke about Vioxx® and this year he is speaking about Celebrex®. Fortunately, there is only one negative study. He does not know what prevention will show, but it was reported that patients that take higher doses of Celebrex® (400mg or 800mg) have a higher risk of cardiovascular complications. All of the other studies with Celebrex® suggest that it is one of the safest NSAIDs available. After reviewing the current data, the FDA voted to maintain access to Celebrex®. The FDA advisory panel, which conducted regular scientific reviews of selective and nonselective pain medications, completed a comprehensive review of this class. The final panel recommended that across the NSAID class, new black box warnings should added to all of the PI's. This warning was added to all selective Cox-2 pain medications as well as the other older nonsteroidal anti-inflammatory (NSAID) drugs such as Naproxen (sodium and ibuprofen). Dr. Montero noted that Celebrex® was sustained after many studies that showed it is safe. He stressed that Celebrex does not interfere with Aspirin and anti-platelet activity like ibuprofen. Dr. Montero's final recommendation was that patients and physicians review all the data. His opinion is that Celebrex® is still the best choice of NSAID, which he believes is supported by the current data.

Dr. Axelrod asked if anyone had any questions. There were none.

Laurie J. Cooksey, Pharm.D., Clinical Pain Specialist and Assistant Clinical Professor from VCU Medical Center discussed Cox-2 Inhibitors

Dr. Cooksey believes that Celebrex is an important drug for certain populations. GI safety is the main issue with patient safety. The most revealing new study is a systematic review and meta analysis where 40,000 patients were evaluated. The population had Osteoarthritis (OA) and Rheumatoid arthritis (RA) patients, they were evaluated specifically comparing Celebrex with Tylenol, placebo and with other NSAIDs. The study reviewed at discontinued rates because of adverse events such as GI adverse events, GI tolerability, clinical ulcers, bleeds as well as the related outcomes. Within all these trials across the population of 40,000 patients, statistically Celebrex showed a benefit in terms of adverse events, GI adverse events, tolerability clinical ulcers and bleeds. This proves the GI safety base of these drugs. Dr. Cooksey noted that there is a new study in the general Managed Care Pharmacy, casts some doubt on the safety findings. Dr. Cooksey clarified that this was a retrospective review based on pharmacy profiles and charts were never reviewed within this trial. Although it is interesting data, the review of COX-2 drugs and patient treatment cannot be based on this trial. She stressed that the goal today is to define the patient population for which the COX-2 class is beneficial and initiate use accordingly.

Dr. Axelrod asked if there was an algorithm to score risk for the Cox-2 Inhibitors. Dr. Cooksey replied that algorithms are available and she could provide those to the Committee. Dr. Axelrod asked if it is similar to the Stanford scoring. Dr. Cooksey replied, yes, it is.

Dr Axelrod asked if there were any other questions. There were none.

MARK OLEY REVIEWED COX-2 INHIBITORS

A lot has occurred in this class over the last year, leaving Celecoxib (Celebrex®) as the only remaining COX-2 agent on the market. Rofecoxib (Vioxx®) was removed from the market September 30, 2004 and Valdecoxib (Bextra®) was removed from market on April 7, 2005, following a February 2005 meeting of

the FDA advisory panel, which conducted a rigorous scientific review of selective and non-selective pain relievers. The panel recommended that stronger warnings be added to all selective COX-2 pain medicines as well as to the older, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen. The final label contains a boxed warning of potential cardiovascular and gastrointestinal risks for Celebrex® that is consistent with warnings for other prescription pain relievers. In addition, the panel recommended avoiding usage of all NSAIDs and Cox-2 selective medicines to treat the acute pain associated with heart by-pass surgery. The final label now includes a boxed warning of potential cardiovascular and gastrointestinal risks.

Celebrex® made by Pfizer received a new indication on July 29, 2005 and is now approved to relieve the signs and symptoms associated with ankylosing spondylitis.

Mark Oley motioned to keep the COX-2 inhibitors class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Proton Pump Inhibitors

Michael Dillon, R.Ph., Scientific Affairs Liaison for Santarus, Inc discussed PPI ~ Zegerid®
Mr. Dillon noted that Zegerid® is an immediate release formulation of omeprazole. It is the first and only immediate-release proton pump inhibitor. It utilizes technology, licensed by Santarus from the University of Missouri, which delivers omeprazole without the need for enteric coating. PPIs are acid labile. Until recently, all of the marketed formulations of PPIs used an enteric coating, which made them delayed release products. Zegerid® is a combination of micronized omeprazole and NaHCO3, which is available as 20mg and 40 mg powder for suspension. Oral capsule and chewable tablet formulations are under development. Zegerid® was approved by the FDA on June 15, 2004. Zegerid® may not be substituted with other omeprazole products, either branded or generic. Studies demonstrated that after the first dose was given before breakfast, Zegerid® 20mg raised gastric pH to 7 and reduced the volume of gastric acid secretion by 50% at breakfast and 80% at dinner. Mr. Dillon stated that proton pump inhibitors are only effective in active proton pumps. Zegerid achieves its peak plasma concentration within 30 minutes. Zegerid may be administered via nasogastric or orogastric tube, in addition to oral administration of the suspension. Zegerid® is approved for the treatment of duodenal ulcer, symptomatic GERD, erosive esophagitis, maintenance of healing of erosive esophagitis, treatment of active benign gastric ulcer, and reduction of risk of upper GI bleeding in critically ill patients. A study of night time acid suppression found Zegerid® 40 mg QD, 20 mg and 40 mg BID with or without food are superior to pantoprazole 40 mg QD and BID in maintaining night time pH control. Zegerid® received approval from the FDA for the reduction in risk of upper GI bleed in critically ill patients. It is the only marketed PPI – even considering IV formulations – with this indication. Populations that may benefit from this product include patients experiencing problems with nocturnal acid control, taking supplemental acid control products (H2RAs and antacids) or BID PPI therapy, with compliance issues or dysphagia, critically ill patients at risk of UGI bleeds, and those receiving compounded PPI preparations.

Mark Henderson, PhD, Medical Information Scientist for AstraZeneca discussed PPIs ~ Nexium
Dr. Henderson reviewed a study published earlier this year evaluating erosive esophogitis and comparing Esomeprazole (Nexium®) and Pantoprazole (Protonix®). The patient population (over 3,000) had history of GURD for greater than 6 months and suffered heartburn at least 4 to 7 consecutive days before being enrolled in the study. The primary end point was healing of the Erosive esophogitis by week eight. The study was multi-centered, double blinded and randomized with attention to three populations. Nexium® 40mg healed the greater percentage of patients compared to Protonix® at week 4 and week 8.
Dr. Henderson then reviewed a study that evaluated Nexium® and risk reduction of NSAID-Associated Gastric Ulcer Indication. Within this study two multi-center, double-blind, placebo-controlled studies were conducted in patients at risk of developing gastric and/or duodenal ulcers associated with continuous use of non-selective and COX-2 selective NSAIDs. A total of 1,429 patients were randomized across the two studies. Patients ranged in age from 19 to 89 (median age 66.0 years) with

70.7% female, 29.3% male, 82.9% Caucasian, 5.5% Black, 3.7% Asian, and 8.0% others. At baseline, the patients in these studies were endoscopically confirmed not to have ulcers but were determined to be at risk for ulcer occurrence due to their age (>/= 60 years) and/or history of a documented gastric or duodenal ulcer within the past 5 years. Patients receiving NSAIDs and treated with NEXIUM 20 mg or 40 mg once-a-day experienced significant reduction in gastric ulcer occurrences relative to placebo treatment at 26 weeks. No additional benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg. These studies did not demonstrate significant reduction in the development of NSAID-associated duodenal ulcer due to the low incidence.

Russell C. Bowes III, Ph.D., Manager, Scientific Affairs Liaison for Ortho-McNeil Janssen Scientific Affairs, LLC discussed Rabeprazole (Aciphex®)

Mr. Bowes had three points concerning Aciphex®. The first is that it has the most rapid onset of action of all of the PPIs, which he believes, is due to its high PKA. He reviewed a study from 2005 that evaluated a 24-hour heartburn free interval in a population with moderate to severe gastroesophageal reflux disease. The heart burn relief was higher in the Rabeprazole treated group. Another study he reviewed evaluated the effect of long term maintenance therapy after five years of maintenance therapy in patients treated with Rabeprazole. At the end of five years, the relapse rate in the Rabeprazole treated patients was significantly lower verses placebo. The patient discontinuation rates were higher in the placebo group compared to the Rabeprazole primarily due to clinical relapse. Approximately 87% remained healed after five years verses 20 % healed in placebo. The
five-year safety data did not show a difference between the Rabeprazole group and placebo. On demand therapy was evaluated over a 6 month period in 2004 to review the efficacy of on demand treatment.

Mark Szalwinski reviewed Proton Pump Inhibitors (PPIs)

Mr. Szalwinski noted that there were not a lot changes in this class. Zegerid® (formerly Rapinex) is an immediate-release formulation of omeprazole using sodium bicarbonate instead of an enteric coating to protect the PPI from acid degradation in the stomach. It is indicated for the treatment of duodenal ulcer and the treatment and maintenance of healing of erosive esophagitis. It is manufactured by Santarus. A NDA has been filed for Zegerid® (omeprazole) Capsules 40 mg and 20 mg to be available in the future. Nexium® received a new indication of risk reduction of NSAID-associated gastric ulcers and Nexium has a new IV formulations.

The new generic Omeprazole has been released on the market (generic for Prilosec®). Financial information for this drug will be discussed in the confidential session.

Dr. Axelrod commented that this one of the complicated classes for those eligible for Part D that may continue to have OTC coverage through Virginia Medicaid. He asked how this would be addressed by the Department.

Cheryl Roberts, DMAS, replied that the Department has discussed this potential issue and is working to ensure that not all of the expenses for OTC drugs are transferred to DMAS, particularly when required by plans for step therapy.

Mark Szalwinski motioned to maintain the PPI class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Angiotensin Receptor Blockers (ARBs) (formerly named Angiotensin Receptor Antagonists)

Dr. Albert Magnin, Internal Medicine, for Sankyo Pharma discussed the Angiotensin Receptor Blockers ~ Benicar®

Dr. Magnin discussed olmesartan, Benicar® trade name. It is available in three doses and the starting dose is 20 mg. It is also available in a combination tablet with Hydrochlorothiazide. As with most of the ARBs it is a benign drug and in the pre-marketing trial the placebo was discontinued more often than the olmesartan. He reviewed a study comparing the efficacy and safety of olmesartan (Benicar®) verses losartan (Cozaar®), valsartan (Diovan®) and eprosartan (Teveten®) in a population where the blood pressure was in the mid 150 systolic and diastolic was around 104. Olmesartan in the mean diastolic blood pressure achieved about 11.5mm of mercury drop that was significant greater compared to the other three agents. In the systolic, it achieved a significant greater lowering than the losartan (Cozaar®), valsartan (Diovan®). A large change occurring today is all of the new data reassigning the BP goals and difficulty to achieve these new goals. The new goal of 130/80 does not sound a lot different form the 140/90 but it is a major change. Olmesartan, 24-hour monitoring system, achieved a 52.9% success rate of the below 140/90 goal and approximately 30% reached the goal below 130/85. With the goal130/80, approximately 20% reached the goal. The speaker believes that this drug has consistent efficacy and would like to see it continued on the PDL.

Dr. T. Donald Marsh, Associate Director, Medical Science Liaison Group from Kos Pharmaceuticals, Inc. discussed the Angiotensin Receptor Blockers ~ Teveten and Teveten/HCT

Dr. Marsh discussed eprosartan (Teveten®) and focused on a recent study, the MOSES study. The study population was secondary stroke patients. This study compared eprosartan to a beta blocker used in Europe. Dr. Marsh distributed a handout to the Committee that he reviewed. The handout's major points were: 1) eprosartan significantly and similarly lowers and maintains blood pressure over time in a high-risk patient population, 2) compared with the calcium channel blocker nitrendipine, eprosartan provides additional benefits in CVA and cardiovascular out comes, and 3) these benefits are achieved beyond the blood pressure lowering.

Mark Henderson, PhD, Medical Information Scientist from AstraZeneca discussed the Angiotensin Receptor Blockers ~ Atacand®

Dr. Henderson reviewed Atacand®, which was initially approved for the treatment of heart failure in March of 2005 and revised in April of 2005. The summary bases for approval were the CHARM Alternative and CHARM added trials. Candesartan was studied in two heart failure outcome studies: 1) The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity trial in patients intolerant of ACE inhibitors (CHARM-Alternative) and 2) CHARM-Added in patients already receiving ACE inhibitors. Both studies were international double-blind, placebo-controlled trials in patients. In both trials, patients were randomized to placebo or Atacand® (initially 4-8 mg once daily, titrated as tolerated to 32 mg once daily) and followed for up to 4 years. The primary endpoint in both trials was time to either cardiovascular death or hospitalization for heart failure.

CHARM-Alternative included 2,028 subjects not receiving an ACE inhibitor due to intolerance. The mean age was 67 years and 32% were female, 48% were NYHA II, 49% were NYHA III, 4% were NYHA IV, and the mean ejection fraction was 30%. Sixty-two percent had a history of myocardial infarction, 50% had a history of hypertension, and 27% had diabetes. After a median follow-up of 34 months, there was a 23% reduction in the risk of cardiovascular death or heart failure hospitalization on Atacand®, with both components contributing to the overall effect.

In CHARM-Added, 2,548 subjects receiving an ACE inhibitor were randomized to Atacand® or placebo. The specific ACE inhibitor and dose were at the discretion of the investigators, who were encouraged to titrate patients to doses known to be effective in clinical outcome trials, subject to patient tolerability. Forced titration to maximum tolerated dosed of ACE inhibitor was not required.
The mean age was 64 years. The mean daily dose of Atacand® was approximately 24 mg and 61% of subjects on treatment received 32 mg once daily. After a median follow-up of 41 months, these was a 15% reduction in the risk of cardiovascular death or heart failure hospitalization on Atacand® (p=0.011),

with both components contributing to the overall effect. There was no evident relationship between dose of ACE inhibitor and the benefit of Atacand®. In these two studies, the benefit of Atacand® in reducing the risk of CV death or heart failure hospitalization was evident in major subgroups and in patients on other combinations of cardiovascular and heart failure treatments, including ACE inhibitors and beta-blockers.

Gill Abernathy asked Dr. Henderson to repeat the patient population of the study of the CHARM-Added. Dr. Henderson answered that everyone in this study were on standard of care, which means that 100 % were on ACE inhibitors, 60 % were also on Beta Blockers, and almost everyone was on a diuretic.

Gill Abernathy asked about the stage of the population. Dr. Henderson answered NYHA CLASS II to IV.

Dr. Ray Lancaster, Pharm. D. from Novartis Pharmaceuticals discussed the Angiotensin Receptor Blockers ~ Diovan

Dr. Ray Lancaster distributed a summary page for the Committee. He made three points: 1) FDA has approved Diovan for the reduction of cardiovascular death in patients at high risk (with left ventricular failure or left ventricular dysfunction) following a heart attack. These patients represent 80% of the mortality post-heart attack.; 2) there was a small study published in 2005 comparing the efficacy of valsartan (Diovan®) verses olmesartan (Benicar®) in mild to moderate hypertension. This was a probe study and the end of the study showed equivalent efficacy, although a numerically superior blood pressuring lowering for valsartan (Diovan®) verses olmesartan (Benicar®).; and 3) one other trial done in African Americans with a fixed dose of valsartan HCTZ, a lowered peripheral edema and even lower joint swelling was seen.

Mark Szalwinski reviewed Angiotensin Receptor Blockers (ARBs) (formerly named Angiotensin Receptor Antagonists)

Mr. Szalwinski noted that there were no new products and a few new indications in this drug class. Hyzaar® is now indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH), but there is evidence that this benefit does not apply to all populations. Diovan® has a new indication to reduce cardiovascular death in patients at high risk (with left ventricular failure or left ventricular dysfunction) following a heart attack. The FDA also expanded the drug's heart failure labeling. Diovan can now be prescribed in a broader range of heart failure patients and is no longer limited to those intolerant of ACE inhibitors.

Atacand® was given the FDA labeled indication of “Approved” as add-on therapy for patients already on an ACE inhibitor. The FDA approved the new and beta blocker in treating class II to IV heart failure and left indication (05-18-05) ventricular dysfunction. Having an added effect on these outcomes when used with an ACE inhibitor based on the CHARM study.

Mark Szalwinski motioned to maintain the Angiotensin Receptor Blockers (ARBs) (formerly named Angiotensin Receptor Antagonists) class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)

Danny Icenhour, Pharm.D., Director, Professional Information Services for King Pharmaceuticals Inc. discussed ACE Inhibitors ~Altace® (ramipril)

Dr. Icenhour reviewed the HOPE 2 studies. He reminded the Committee that the original HOPE study demonstrated that ramipril (Altace®) 10mg daily for 4.5 years reduced vascular events and new diagnosis of diabetes. The HOPE 2 study was a 2.6 year extension to determine where the cardiovascular and metabolic benefits of ramipril were maintained, and if other groups could benefit from treatment. In conclusion, the benefits of ramipril observed during the access period maintained for cardiovascular

deaths, stroke, and hospitalization for heart failure. Additional reduction of MI revascularization and new onset diabetes were also observed. Benefits of ramipril were additive to those of other life saving therapies that included all patients.

Mark Oley reviewed Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)
Aceon® made by Solvay, received a new indication for the treatment of patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction (MI).

Mark Oley motioned to maintain the Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors) class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Inhaled Corticosteroids

Gokul Gopalan, MD, MPH, Medical Science Specialist for Schering-Plough Pharmaceuticals discussed Inhaled Corticosteroids ~ Asmanex
Dr. Gopalan noted that the prevalence and associated mortality of asthma has been treated in the past decade across all segments of the population. Inhaled corticosteroids are recommended first line for the treatment of mild to moderate and severe persistent Asthma. There are several studies that show continued use of these products provide superior Asthma control and decrease exacerbation in hospitalizations or asthma attacks. Inhaled Asmanex® (mometasone furoate) was approved for the treatment of asthma as the first inhaled asthma drug. It is the only corticosteroid FDA approved for once daily treatment of asthma symptoms. It provides 24-hour therapeutic benefit. Asmanex® has a high penetration to the site of action. Mometasone furoate is an inhaled corticosteroid approved for once- or twice-daily administration. Once-daily administration of mometasone furoate appeared safe and effective in children and adults 12 years of age and older with mild to moderate persistent asthma. Asmanex® has the lowest systemic or total bioavailability across the inhaled corticosteroid class, showing about 1% systemic absorption. All comparative studies have been short-term and establish that mometasone is as effective as twice-daily administered beclomethasone, budesonide, and fluticasone, and more effective than once-daily budesonide in adolescent and adult patients with mild to moderate persistent asthma. As a device, Asmanex® is unique in that it is a cap activated (turning the cap primes the next dose), breath actuated DPI with a built-in usage counter.

Erin Drew, Regional Medical Scientist for GlaxoSmithKline discussed Inhaled Corticosteroids ~ Advair® and Flovent®

Ms. Drew stated that as the last speaker noted the gold standard care for asthma could be achieved simply by using inhaled corticosteroids. The goals are no chronic symptoms, minimal use of rescue drugs, and no exacerbations. It is clear from research services that many Medicaid patients are not reaching these goals of therapy. GSK is part of a global commitment to improve the air environment they have eliminated all of the CFC propellants from their inhalers and are now using all non-propellant formulations. The new inhalers have the same efficacy and safety without the CFC propellants for patients who are not controlled on mild corticosteroids.

Kevin Cooper, MD, Pulmonologist from MCV/VCU School of Medicine discussed Inhaled Corticosteroids ~ Advair
Dr. Cooper works for the MCV asthma clinic and was not paid by a pharmaceutical manufacturer for his presentation. His goal is better asthma control for this specific population. The clinic has been extremely successful and has cut the overall cost of treating asthma to this population by over one-half. Advair® has been a cornerstone of that treatment at the clinic for the vast majority. Almost every patient is using Advair® at the clinic. When inhaled corticosteroids are not enough, a long acting broncodilatation needs to be added. Advair® is the only product to incorporate both types of drug into this combination. Advair® maintains ease of use it is just one puff twice a day and assures that the patient will not be without of either medication. Advair® is an expensive medication but it has been shown to save money

because it decreases over all health care cost. Advair® is an important therapy, which is also approved for the management of COPD and useful at improving the management of this disease.

Mark Oley reviewed Inhaled Corticosteroids
Mometasone (Asmanex® Twisthaler) became available on March 30, 2005 and is manufactured by Schering. Mometasone furoate is an inhaled corticosteroid approved for once- or twice-daily administration. Once-daily administration of mometasone furoate appeared safe and effective in children and adults (12 years of age and older) with mild to moderate persistent asthma. As a device, Asmanex® is unique in that it is a cap activated (turning the cap primes the next dose), breath actuated DPI with a built-in usage counter. Another ICS DPI product on the market is the Pulmicort® Turbuhaler. Each inhaler is supplied in a protective foil pouch. The inhaler should be discarded 45 days after opening the foil pouch or when dose counter reads "00", whichever comes first. As the dry powder contains milk proteins, it is important to note that Asmanex® is contraindicated in patients with known hypersensitivity to any of the product ingredients, including lactose or milk proteins.

Dr. Axelrod asked the Committee members who work at hospitals if many people were being discharged from the hospitals with Advair. The response was, yes, they were.

Mark Oley motioned to maintain the Inhaled Corticosteroids class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Nasal Steroids

Gokul Gopalan, MD, MPH, Medical Science Specialist for Schering-Plough Pharmaceuticals discussed Nasonex®
Dr. Gopalan reviewed Nasonex® and its indication for allergic rhinitis. Nasonex® or intranasal mometasone furoate monohydrate is for the treatment of allergic rhinitis. Allergic rhinitis affects between 25 and 45 % of the population and is the number one chronic condition in the pediatric population. Intranasal corticosteroids should be considered for first-line therapy of allergic rhinitis. Compared to antihistamines, decongestants, and mast cell stabilizers, intranasal corticosteroids have the following positive effects: (1) they suppress late phase allergic reactions and at least attenuate early phase reactions; (2) they are as effective as oral corticosteroids; (3) they reduce all nasal symptoms; and (4) they relieve upper airway inflammation that reduces seasonal asthma and decreases bronchial hyperactivity. Nasonex® is the most potent intranasal corticosteroids with the highest receptor bind affinity of any corticosteroids. Nasonex is safe. No growth suppression has been seen. It can be used down to 2 years of age. Product Insert updates including new FDA approved indication and data for the treatment of nasal polyps in patients 18 years and older. (Reference: Nasonex PI update, 12/04) The Nasal Polyposis study has been accepted for publication in peer reviewed journal, The Journal of Allergy and Clinical Immunology (JACI) October/November 2005. [Stjärne et al. "A Randomized Controlled Trial of Mometasone Furoate Nasal Spray in Nasal Polyposis". New Scent Free Formulation and supporting preference study results. Meltzer et al., Treat Respir Med. 2005: 4 (4) 289-296] Respiratory Medicine is an international peer-reviewed journal that provides comprehensive coverage of the management of a wide range of respiratory disorders. The journal publishes topical, critical reviews and high-quality original clinical research relating to the use of drugs, devices, diagnostics and other interventions for the treatment of patients with respiratory disorders.

Mark Szalwinski reviewed Nasal Steroids
Mr. Szalwinski noted that there were no significant changes to this class from last year.

Mark Szalwinski motioned to maintain the Nasal Steroids class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Beta Adrenergics

Karen Rance MSN, CPNP, AE-C, Practicing pediatric nurse practitioner/Certified asthma educator from Tidewater Pediatric Consultants reviewed Beta Adrenergics ~ Levalbuterol (Xopenex®)

Ms. Rance is a certified asthma educator in Virginia Beach. She practices in a large urban primary care pediatric practice. Her practice is 50% Medicaid and 85% African American. She highlighted three studies that she believes support the use of Levalbuterol (Xopenex®). There are only two short acting Beta Adrenergics available, albuterol and Levalbuterol. Levalbuterol is the R (-)-enantiomer of racemic albuterol. All the bronchodilating activity of commercially available racemic albuterol resides in this isomer, which is the active $beta_2$-receptor agonist. The S (+)-enantiomer does not bind to $beta_2$-adrenoceptors, but may be responsible for some adverse effects of racemic albuterol, including bronchial hyper-reactivity and reduced pulmonary function during prolonged use. Levalbuterol provides a reasonable treatment alternative for patients in whom albuterol or another $beta_2$-agonist is effective but who experience significant adverse effects. Two of the studies she reviewed were specifically focused at children. In both studies, Levalbuterol (Xopenex) was shown to be effective and safe in children with few side effects. Her opinion from the studies she presented was that the presence of the S (+)-enantiomer can reduce the binding of the more effective R (-)-enantiomer.

Mark Szalwinski reviewed Beta Adrenergics

Xopenex® HFA is a metered-dose inhaler formulated with hydrofluoroalkane (HFA), a non-chlorofluorocarbon (CFC) propellant. It is indicated for the treatment or prevention of bronchospasm in adults, adolescents and children (4 years of age and older) with reversible obstructive airway disease. FDA approved new formulation of the drug Xopenex on March 11, 2005 and it has been available since March 25, 1999 in a solution for nebulization.

Mark Szalwinski motioned to maintain the Beta Adrenergics class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

COPD Anticholinergics

Kevin Cooper, MD, Internal Medicine /Pulmonary Disease/ Preventive Medicine & Community Health for VCU Health System discussed COPD- Anticholinergics ~ Spiriva®

Dr. Cooper reviewed Spiriva. A new study in last month's Annals of Internal Medicine (entitled "Prevention of Exacerbations of Chronic Pulmonary Disease with Tiotropium, a Once-Daily Inhaled Anticholinergic Bronchodilator." Ann Intern Med., Sept 2005; 143:317-326) refers to tiotropium (Spiriva®) versus ipatropium (Atrovent®). This study took place in the 26 Veterans Administration (VA) hospitals around the country including the VA Medical Center (McGuire) in Richmond. In the study, they documented that after the use of Spiriva for a period of one year, there was a decrease of acute acerbations of COPD, hospitalizations for COPD, and unscheduled clinic visits for COPD. The second was a symposium and it showed that Spiriva® significantly improved the FEV1 for over 24 hours after a single inhalation. Dyspnea was decreased, health related quality of life was improved, and hospitalization was reduced. People have actually contacted Dr. Cooper after taking Spiriva® to thank him because it made such a difference in their health.

Mark Szalwinski reviewed COPD Anticholinergics *(formerly included with Beta Adrenergics)*

This class consists of two agents, Ipratropium bromide (Atrovent®, Atrovent HFA®) and Tiotropium bromide monohydrate (Spiriva®). Both agents are FDA approved for maintenance treatment of bronchospasm associated with COPD. Ipratropium is available as a Metered Dose Inhaler (MDI) and an inhaled solution – as a single agent and in combination with albuterol; tiotropium is only available as a Dry Powder for Inhalation (DPI). Ipratropium and tiotropium have similar onsets (15 minutes vs. 30 minutes) and times to peak effect (1 to 2 hours vs. 1.5 to 3 hours). The slightly quicker onset for

ipratropium is not considered a distinguishing feature as these agents are used chronically and should not be used as rescue therapy.

The most significant difference between the agents (other than formulations available) is in the duration of the bronchodilator effects. Significant bronchodilation following ipratropium inhalation lasts for 3 to 4 hours in most patients and may persist for up to 6 hours in some. Bronchodilation following tiotropium inhalation is observed for 24 hours or longer. Contraindications, warnings, adverse drug events, and drug interactions are similar for the inhaled anticholinergic agents and are considered class effects. Spiriva® was released in January 30, 2004. Atrovent® was first released in December 29, 1986 as a MDI. Ipratropium is also found in combination with albuterol and is known as Combivent ® and Duoneb®. Both of these products have been reviewed before and have not changed, they are just being reclassified.

Mark Szalwinski motioned to maintain the COPD Anticholinergics class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Beta Blockers

Kerry Cunningham, Regional Medical Scientist for GlaxoSmithKline discussed Beta Blockers ~ Coreg®

When compared to metoprolol tartrate in the COMET study, carvedilol statistically reduced overall mortality by a relative risk reduction (RRR) of 17%. This reduction in mortality seen with carvedilol was statistically significant in death due to stroke, CV death, and sudden death (American Heart Journal 2005; 149: 370-6). Carvedilol is the only beta blocker FDA indicated and recommended by The American College of Cardiology and American Heart Association (ACC/AHA) in the recently updated 2005 Heart Failure Guidelines for the treatment of Stage A, B and C heart failure patients. Coreg remains the only beta blocker to be indicated for mortality reduction post-MI with left ventricular dysfunction as seen in the CAPRICORN study. Data recently published from this study shows that carvedilol is also effective in reducing atrial and ventricular arrhythmias following a MI (Journal of the American College of Cardiology (JACC); 45 (4).

Mark Szalwinski reviewed Beta Blockers

Mr. Szalwinski noted that there were no significant changes with this class at this time but a recently published study has brought attention to established prescribing practices. Atenolol has been shown to improved post-infarction survival and decreasing the incidence of nonfatal cardiac arrest and cardiac death as well as reducing all-cause mortality. A study in Lancet published on September 10, 2005 showed BP lowering of 10mm Hg compared to placebo. The study also showed a significantly higher mortality (1.13 [1.02-1.25]) with atenolol treatment than with other active treatment. This multi-center study was comprised of 17,671 patients who were followed up for a mean of 4.6 years. Cardiovascular mortality and stroke tended to be higher with the atenolol treatment group. More will need to be done with this information before responding as the authors' methods, findings, and interpretation have not yet been subject to the rigorous scrutiny of the medical community. The Committee will follow it closely to determine how and if it affects the PDL.

Mark Szalwinski motioned to maintain the Beta Blockers class as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Mark Szalwinski reviewed Calcium Channel Blockers

Mr. Szalwinski noted that there were not a lot of changes in the Calcium Channel Blockers class. The product Diltiazem has a new indication to include arrhythmias and PSVT.

Mark Szalwinski reviewed H2 Antagonists

Mr. Szalwinski noted that there was no real change to this class from last year.

Mark Szalwinski reviewed Second Generation Antihistamines (LSAs)
Mr. Szalwinski noted that there have been a few changes in this group. The changes revolve around new generics or new dosage forms, like rapidly disintegrating tablets. The newest, Fexofenadine, is the generic of Allegra® and is now available.

Mark Szalwinski reviewed Sedative Hypnotics (Benzodiazepine)(*formerly included with Sedative Hypnotics)*
The Sedative Hypnotics class has been divided into two classes for review, the classes are, Sedative Hypnotics (Benzodiazepine) and Other Sedative Hypnotics (non-Benzodiazepine). Within the Sedative Hypnotics (Benzodiazepine) class, there have been no changes.

Mark Szalwinski motioned to maintain all of these classes (Calcium Channel Blockers, H2 Antagonists, Second Generation Antihistamines, and Sedative Hypnotics (Benzodiazepine) as PDL eligible. This motion was seconded and unanimously approved by the Committee.

Other Sedative Hypnotics (non-Benzodiazepine)(*formerly included with Sedative Hypnotics)*

Teresa Cozza, Regional Scientific Manager for Takeda Pharmaceuticals America, Inc. discussed Other Sedative Hypnotics ~ Rozerem®
Dr. Cozza discussed Rozerem®, generic name of Ramelteon. This is the first and only non-scheduled hypnotic that is FDA approved for the treatment of insomnia. The Benzodiazepine and non-Benzodiazepine receptor agonist are all schedule 4 control substances. All of theses formulations are non-narcotic by definition; however, they do remain under the juristic of the DEA as they are controlled substances. Rozerem® is not a Benzodiazepine receptor agonist and in addition to not being controlled, it does not suppress the central nervous system. It has a unique mechanism of action, a melatonin receptor agonist (MT_1 and MT_2 receptors). It targets the underlying pathophysiology of the sleep wake cycle. MT_1 and MT_2 receptors sites are believed to be responsible for the feelings of sleeplessness and assisting the body from adjusting from day to night. Rozerem does differ from Melatonin in its chemical structure, its selectivity, affinity and its proven safety and efficacy profile. Dr. R. Griffiths of Johns Hopkins University conducted the abuse liability studies with Rozerem using up to 20 times the recommended dose. The results show that Rozerem has no abuse potential, no effect on cognitive performance, and no affect to behavioral performance. In addition, there were no clinically meaningful differences verses placebo on standard measures balance, memory, and the ability to concentrate. There has been no evidence of rebound or withdrawal upon discontinuation of Rozerem. Rozerem is approved for long term use. The CYP1A2 system is the major isoenzyme involved in metabolism of Rozerem, there is no dosage adjustment necessary based on age, renal function, hepatic function, mild to moderate COPD, and sleep apnea. The most common side effects seen with Rozerem include headache, dizziness, somulance, and fatigue. The primary outcome of latency to persistent sleep was significantly shorter in the study group (shorter latency) compared to placebo. In addition, the study group experienced significantly longer total sleep time but wake time after sleep onset and time spent in each sleep stage were not significantly different from placebo.

Mark Oley asked how this differs from the OTC version of melatonin. Dr. Cozza answered that there are a number of differences. First, Rozerem® is different chemically in a way that allows the structure to be more stable, so there is a longer half life. In addition, the NIH recently published a finding that says melatonin was not found to be efficacious in sleep induction. With Rozerem®, there is proven efficacy and safety with the FDA.

Mark Szalwinski asked how the efficacy was demonstrated. Dr. Cozza answered that there have been both transient sleep studies in labs and in the chronic insomniac population. There have been a total of 7 clinical trials, in both the adult and elderly populations. In addition to safety studies that have included specialty populations such as impaired renal function, impaired hepatic function, mild to moderate

COPD and sleep apnea. In these studies, the sleep latency has been decreased and the total sleep time increased.

Gill Abernathy asked that since this drug has only been available a few months, if any national groups have made any statements on this relative to any other available agents. Dr. Cozza answered no, this drug was approved in July and has been widely available on formularies as of September.

Mark Szalwinski asked if the drug was only compared to placebo. Dr. Cozza answered, yes, it is compared to placebo in all of the published studies. There is one long-term open label study that is not yet published which was conducted over one year. Total sleep time was increased at 6 months by one hour and 1.15 hours at 12 months.

Mark Szalwinski asked if all of studies required 2 to 4 times the dosage from what published in the package insert. Dr. Cozza answered, no, the studies varied. The information given is based on the 8 mg that is being marketed. There were dosage ranging studies that evaluated from 4 mg to 54 mg. The 8 mg dose was found to have the most consistent efficacy dose across all studies. The abuse liability studies were done at 20 times the recommended dose, which was 160mg.

Dr. Axelrod asked the next speaker to be Dr. Neubauer to help answer these questions. He also asked if Dr. Neubauer was the PI. Dr. Neubauer replied that he was not a PI for this product.

Dr. Dhillon asked if were prolactin levels were impacted transient. Dr. Cozza answered that in the 6 month trials the prolactin levels were transiently increased in terms of their mean and they did remain within normal limits. There were no clinical correlations with the increase. Dr. Neubauer replied that the mean stayed with in the normal reference range. Although it was significantly different from Placebo, it was not outside of the range.

Dr. Selby-Penczak asked the ages of the elderly population studied. Dr. Cozza answered that the adult population was from ages 18 to 64 and the elderly was 65 to 98 years of age.

Dr. Axelrod commented that this is obviously an important drug, particularly for the population impacted by Part D. The use of sedative hypnotics for the elderly in LTC facilities is high. The cognitive impact of some of the agents has always been an issue; patients get sleep but lose the cognitive function.

Mark Oley asked them to explain again how Rozerem® differs from the OTC version of melatonin in relation to the circadian rhythm? Dr. Cozza answered that information concerning Rozerem and its effect on circadian rhythm is not readily available at present. Dr. Cozza asked Dr. Neubauer if he could elaborate.

Dr. Neubauer answered that the first issue is that melatonin is not regulated at all and no one is really sure what is purchased OTC at the health food store. Rozerem has been thoroughly evaluated for safety and efficacy, the structure is different, the binding is different. It is selective M1 and M2, and it does not touch M3, which is in other tissues around the body. This is another advantage. The metabolism is different melatonin that has some products including some that affect the serotonin system. The active metabolite of Rozerem® has a relatively short half-life.

Dr. Selby-Penczak asked what numbers of elderly were studied. Dr. Cozza answered that in this study 878 elderly were studied.

David N. Neubauer, M.D., Associate Director, Johns Hopkins Sleep Disorders Center and Assistant Professor, Department of Psychiatry & Behavioral Sciences for Johns Hopkins University School of Medicine discussed Other Sedative Hypnotics ~ Ramelteon (Rozerem®)

Dr. Neubauer reviewed the history of sleep products. He noted that getting to sleep was never the issue with products like laudem and chloralhydrate, safety has always been the issue. He reviewed a handout with the Committee and reviewed a few of the studies noted in the handout. He stressed that what sets this product apart from other products in the same class today is the safety profile and the lack of addictive properties. See reference below for articles referenced:

- Griffiths RR and Suess, P. Ramelteon (TAK-375) and triazolam in humans: behavioral effects and abuse potential. American Psychiatric Association 2005 Annual Meeting New Research Abstracts. 2005:76-77.
- Roth, T, Seiden, D, Sainati, S, Weigand, S, Zhang, J, and Zee, P. Phase III Outpatient Trial of Ramelteon for the Treatment of Chronic Insomnia in the Elderly. J Am Geriatr Soc. 2005;53(4), S25.
- Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-Receptor Agonist, Reduces Latency to Persistent Sleep in a Model of Transient Insomnia Related to a Novel Sleep Environment. Sleep. 2005;28(3): 303-307.
- Zammit, G, Roth, T, Erman, M, Sainati, S, Weigand, S, and Zhang, J. Polysomnography and outpatient study to determine the efficacy of ramelteon in adults with chronic insomnia. American Psychiatric Association 2005 Annual Meeting New Research Abstracts. 2005:227.
- Zammit, G, Roth, T, Erman, M, Sainati, S, Weigand, S, Zhang, J. Double-blind, placebo-controlled polysomnography and outpatient trial to evaluate the efficacy and safety of ramelteon in adult patients with chronic insomnia. Sleep. 2005;28:A229.

Gill Abernathy asked Dr. Neubauer about his work at Johns Hopkins. Dr. Neubauer stated that he practices sleep medicine and Psychiatry.

Dr. Axelrod asked about the duration of therapy for Rozerem. Dr. Neubauer answered that it is simply indicated for the treatment of insomnia characterized by difficulty with sleep onset. There is an implication that it should be limited to short term.

Dr. Axelrod asked how long the studies were on duration of therapy. Dr. Neubauer answered that he is aware of the 5 week studies mentioned in his references and he believes that there is a 6 month trial is currently being conducted.

Dr. Dhillon asked if after a time a person needed a higher dose than the 8 mg. Dr. Neubauer answered, no, since this drug has no sedating affect, the benefits would happen with that same 8 mg dose. There is no recommendation to increase the dose.

Dr. Dhillon asked what the recommendations were in relation to Fluvoxamine. Dr. Neubauer answered that it is recommended that Fluvoxamine not be used in combination with Rozerem. He stated that this was the only contraindication because of the drug-drug interaction.

Mark Szalwinski asked if the same population was used in the double blind studies or if there were two different populations. Dr. Neubauer answered that he believed that they were done parallel and that it was not the same population.

Mark Szalwinski asked how it is known that there was a difference between the two agents and that the comparative group did not just have a baseline onset of different sleep onset times. Dr. Neubauer answered that the baselines were the same for both groups.

Dr. Beveridge asked the Chairman for more information and studies on this medication to review them. Dr. Axelrod said, yes, more information would be obtained and shared with the Committee.

Mark Szalwinski commented that he believed that the drug to drug interaction studies are probably just occurring. Dr. Neubauer answered that the studies have looked for the predictable interactions, considering that there are several different metabolic pathways. While the 1A2 is the primary, there are other systems that metabolite and there is relatively low potential for interaction. Since this is not a sedating drug, the cumulative CNS suppression will not occur.

Mark Oley asked if this drug has been available in Europe. Dr. Neubauer answered no, it has not. This is the first release of the medication.

Dr. Axelrod asked if it was available in Europe at all. Dr. Neubauer answered no, it is not.

Dr. Beveridge asked if it was available in Japan. Dr. Cozza answered that it is only available in the United States.

Gill Abernathy asked when it actually became available in the drug stores and used by patients. Dr. Neubauer answered the end of September.

Dr. Axelrod commented that the Committee needs more information before the Committee can make decisions for the January 1, 2006 implementation. He requested a date change for the implementation of this class on the PDL. There was some discussion and the Committee decided to complete the class review and revisit the implementation date.

Susan M. Skolly, PharmD, DABAT, Senior Medical Liaison for Sepracor Medical Affairs discussed Other Sedative Hypnotic ~ Lunesta

Dr. Skolly noted that Lunesta was approved by the FDA(December 15, 2004) for the treatment of insomnia in patients 18 years and older. Lunesta®'s chemical name is Eszopiclone. Eszopiclone's effect is believed to result from its interaction with GABA receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. Dr. Skolly noted that Eszopiclone has been shown through 6 placebo controlled and one open label study to be safe and efficacious treatment of transit insomnia in the adult and elderly patients. She noted that a second six month double blind placebo controlled study was recently presented at the American Neurological Association. Dr. Skolly reviewed a two week double blinded placebo controlled study done in elderly patients. Approximately 230 elderly patients were reviewed in the study that demonstrated a clinically significant improvement in sleep onset and sleep maintenance. This is the only medication to receive acknowledgement from the National Institute of Health to be an efficacious long term treatment for adults in the treatment of chronic insomnia in adults.

Paul M. Spector, D.O. , Psychiatrist/Pain Medicine Physician for Sepracor discussed Other Sedative Hypnotics ~ Lunesta

Dr. Spector discussed Lunesta (Ezopiclone), a sedative hypnotic indicated for sleep onset and sleep maintenance. It is the only approved product for long-term use. No development of tolerance to any sleep parameter has been noted in long-term studies and this drug has a low potential for abuse. There is no significant rebound insomnia at doses up to 3mg and no next day residual effects noted in clinical trials. It is a non-narcotic agent with no clinically relevant drug to drug interactions with warfarin, lorazepam or digoxin. Dr. Spector suggested that Lunesta should be added to the current PDL criteria (as preferred) for sedative hypnotics or at least included for elderly patients with sleep disorders and patients with long term use requirements. Dr. Spector also suggested that the same guidelines for authorization should be used as with other non-benzodiazepine agents.

Dr. Spector highlighted the results from the study entitled "A 2-week efficacy and safety study of Eszopiclone in elderly patients with primary insomnia" (Scharf M, Erman M, Rosenberg R, et al. Sleep 2005; 28(6):714-721).

Dr. Beveridge asked if any head to head trials have occurred between Ambien and Lunesta. Dr. Spector answered that he does not believe that any head to head trials have been done.

Dr. Beveridge asked the main reason Dr. Spector preferred Lunesta over the other non-Benzodiazepines. Dr. Spector answered that there are a couple of reasons. Lunesta does not show any cognitive impairment and it is approved for long term use. It is extremely effective and does not leave people with a "hangover".

Danny Icenhour, Pharm.D., Director, Professional Information Services for King Pharmaceuticals Inc. discussed Other Sedative Hypnotics - Sonata® (zaleplon)

Dr. Icenhour reviewed Sonata®, generic name zaleplon. He reviewed a recently published article from the Sleep Medicine journal entitled "The Long Term Use of Sedative Hypnotics in Older Patients with Insomnia". The objective of this article was to evaluate the long term use of Sonata® in the elderly and the study time period of use was 6 to 12 months. This was an open label, blinded study using almost 500 elderly patients with a mean age of 72.5 years. As compared to baseline, the three sleep phase evaluated latency with persistent sleep duration and number of nocturnal awakenings. All three of these improved significantly during the open treatment phase. The safety profile was similar to other short term studies. The study supports that Sonata® (5 and 10 mg) is safe and effective for the treatment of insomnia in the elderly population.

Mark Oley reviewed Other Sedative Hypnotics (Non-Benzodiazepine ~ *formerly included with Sedative Hypnotics)*

Within the class "Other Sedative Hypnotics (non-Benzodiazepine)", two changes are new to the Committee. On September 12, 2005, Sanofi Synthelabo released Ambien CR. The hypnotic is now approved in an extended-release oral dosage formulation in the strength of 12.5mg. Ramelteon, brand name Rozerem, was released by Takeda Global on July 22, 2005. This is a new agent with a unique mechanism of action, a melatonin receptor agonist (MT1 and MT2 receptors). About 12 Melatonin supplements have been used by shift workers, travelers with jet lag, and those having trouble sleeping due to its effects on insomnia and the circadian rhythm in an OTC formulation. This is the first prescription formulation.

Mark Oley asked if the Committee wanted to wait for more information concerning Rozerem and changes in the drug class. The Committee discussed the need for more information on this class and debated how to manage this class. Mr. Szalwinski asked when the drug Ambien would go generic. The representatives from First Health Services answered that Ambien would go generic in October 2006.

Mark Szalwinski motioned to hold decision making on the Other Sedative Hypnotics (non-Benzodiazepine) class until the Spring P&T meeting, at this time it would be evaluated again when more information is available on Rozerem and changes in the drug class.

This motion was seconded and unanimously approved by the Committee.

POTENTIAL NEW PDL DRUG CLASS

Mark Szalwinski reviewed clinical information for Phosphodiesterase 5 Inhibitor's for Pulmonary Arterial Hypertension:

There is currently only one Phosphodiesterase 5 inhibitor available in the United States for the treatment of pulmonary arterial hypertension (PAH). Pfizer released sildenafil under the brand name of Revatio® in July of this year. Revatio® is available in 20 mg tablets and approved to treat pulmonary arterial hypertension (PAH). It is dosed at 20 mg TID. PAH is a rare and potentially fatal disease, receiving a diagnosis is lengthy and complex. No available pharmacological cure for PAH is currently known.

Treatment is aimed at alleviating symptoms and prolonging survival. The treatment of PAH with Revatio is aimed at improving exercise tolerability.

While this use of sildenafil marketed as Revatio® in (PAH) is new, treatment with Viagra® a similar drug to Revatio® (both sildenafil), has occurred over the past year. Drug to drug issues and side effects seen with sildenafil, marketed as Viagra®, are also expected to be seen with Revatio®. Caution should be used and in some cases, it is contraindicated to use Revatio® in combination with nitrates (e.g., nitroglycerin). The most common adverse effects are headache, flushing, dizziness, diarrhea, dyspepsia, abnormal vision, nasal congestion, rash, and decrease in supine blood pressure. It has not yet been assessed the relationship with the possible eyesight loss (NAION) as it has not yet been assessed in this population.

Mark Szalwinski motioned to make the Phosphodiesterase 5 Inhibitor for Pulmonary Arterial Hypertension class PDL eligible with clinical management guidelines. This motion was seconded and unanimously approved by the Committee.

COMMENTS FROM OFFICE OF THE ATTORNEY GENERAL

Ms. Reatha Kay from the Attorney General's office stated that under the Virginia Freedom of Information Act (FOIA), specifically Virginia Code section 2.2-3711, a public body such as the P&T Committee, may go into a closed session for any of the 33 reasons listed in that statute. The discussion of manufacturer and wholesaler prices is not one of the 33 reasons listed.

She stated the Attorney General strongly supports the principles of open government embodied by the FOIA and believes in the opportunity of the Commonwealth's citizens to witness the operation of government to the fullest extent.

Federal Law 42 U.S.C. 1396r-8(b)(3)(D) requires such pricing information to be kept confidential. On this point, federal law supersedes the Virginia FOIA. Since the P&T Committee must discuss this pricing information as part of its duties, pursuant to federal law a confidential meeting must occur for the consideration of this pricing information she cautioned only this confidential information should be discussed.

Mark Szalwinski made a motion for the P&T Committee to resume the meeting in another room to discuss this confidential information regarding prices charged by the manufacturers and wholesalers of the drug classes discussed at this P&T Committee meeting. This confidential meeting is authorized by Federal Law at 42 U.S.C. § 1396r-8(b) (3) (D) that requires this information to be kept confidential.

This motion was seconded and unanimously approved by the Committee. The meeting adjourned to an executive session.

The Committee returned to the room, a motion was made to resume the meeting. The motion was seconded and unanimously approved by the Committee.

Dr. Axelrod clarified that new drug products that are introduced to the market in a drug class previously reviewed by the P&T Committee and deemed PDL eligible will automatically default to being a "non-preferred" drug that requires a prior authorization.

Dr. Axelrod asked Mark Oley provide the drug status recommendations of the Committee for the annual review for Phase I of PDL Classes as well as new drug classes and new drugs in current classes.

Mark Oley stated that based on the review of new drug classes, the following drugs are recommended to "preferred" (no prior authorization required):

Lipotropics - Non Statins: Fibric Acid Derivatives

GEMFIBROZIL
ANTARA

Lipotropics - Non Statins: Niacin Derivatives
NIASPAN
NIACOR

Urinary Tract Antispasmodics
DETROL LA
DITROPAN XL
OXYBUTYNIN CHLORIDE
OXYTROL
SANCTURA
VESICARE
ENABLEX

Electrolyte Depleters
RENAGEL
PHOSLO
FOSRENOL

Topical Immunomodulators
ELIDEL
PROTOPIC

PDE-5 Inhibitors for Pulmonary Arterial Hypertension
REVATIO

Dr. Axelrod asked the Committee if they would place edits on the PDE-5 for PAH drug class to ensure appropriate prescribing. Mark Oley read the proposed clinical criteria for PDE-5 Inhibitors for Pulmonary Arterial Hypertension:

- Length of authorizations: 1 year
- Diagnosis of Pulmonary Hypertension in patients 18 years of age or older is required.
- The requested medication may be approved if both of the following are true: 1) The prescribing physician is a pulmonary specialist or cardiologist and 2) Client has documented Pulmonary Arterial Hypertension and will be followed by the prescribing physician.
- Document clinically supporting information
- Contraindications where the PA should not be approved: Concurrent use of nitrates (e.g., nitroglycerin) and hypersensitivity to sildenafil

This proposed clinical criteria for PDE-5 Inhibitors was discussed by the Committee and agreed. Mark Szalwinski motioned that the criteria, as written, be used to prior authorize the drug Revatio and that the drug would be “preferred” on the PDL. The motion was seconded and unanimously approved by the Committee.

Mark Oley stated that based on the annual review for Phase I PDL classes, the following drugs are recommended to be “preferred” (no prior authorization required):

High Potency Statins
ZOCOR

HMG CoA Reductase Inhibitors (Statins)
PRAVACHOL
LOVASTATIN
LESCOL XL
ALTOPREV
LESCOL
ADVICOR

Other Lipotropics
ZETIA

ACE Inhibitors
LISINOPRIL
ENALAPRIL MALEATE
CAPTOPRIL
BENAZEPRIL HCL
LISINOPRIL-HCTZ
ENALAPRIL MALEATE/HCTZ
CAPTOPRIL/HYDROCHLOROTHIAZIDE
BENAZEPRIL HCL-HCTZ

Angiotensin Receptor Blockers
DIOVAN
COZAAR
DIOVAN HCT
HYZAAR

COPD Anticholinergics
COMBIVENT
SPIRIVA
DUONEB
ATROVENT AER W/ADAP
ATROVENT HFA

Beta Adrenergics
ALBUTEROL SULFATE
XOPENEX
ACCUNEB
METAPROTERENOL SULFATE

Inhaled Corticosteroids Agents
AZMACORT
AEROBID
QVAR 80MCG
QVAR 40MCG
AEROBID M
ASMANEX
FLOVENT HFA

Nasal Steroids
FLONASE
NASONEX
NASACORT AQ
FLUNISOLIDE

Histamine 2 Antagonists
RANITIDINE HCL
FAMOTIDINE

Benzodiazepine Sedative Hypnotics
TEMAZEPAM
RESTORIL 7.5MG
TRIAZOLAM
FLURAZEPAM HCL
ESTAZOLAM
CHLORAL HYDRATE

Dr. Axelrod noted that with the "Other Sedative Hypnotics", the preferred status of drugs would not be chosen at this meeting. The Committee has requested more information. This class will be discussed at the next meeting to give the Committee the ability to research the new product, Rozerem, further. The current PDL will stay in effect until that time.

Mark Oley recommended that based on the annual review for Phase I drug classes, the "preferred" status of drugs in the following classes will remain the same:
Proton Pump Inhibitors
Calcium Channel Blockers (Dihydropyridine and Non- Dihydropyridine)
Beta Adrenergic/Corticosteroid Inhaler Combinations
Beta Blockers
Second Generation Antihistamines (Low Sedating Antihistamines and Decongestant Combinations)
COX II Inhibitors
Ace Inhibitor – Calcium Channel Blocker
Beta Adrenergics (Short Acting and Long Acting)
Combination HBM and DHPCCB

Dr. Axelrod asked if there was discussion from the Committee following the review of the drug status with each class. There was no discussion unless otherwise noted.

Mark Oley clarified that all new drugs in existing PDL eligible classes discussed during the meeting (Factive®, Zmax™, Clarithromycin (Generic Biaxin®) and Actonel® with Calcium CO-PACK) were recommended to be "non-preferrred" in their respective drug classes

Mark Oley motioned that based on the review of Phase I drug classes, new drugs in current classes (four drugs noted above), and the six new drug classes, that the drug status (preferred or non-preferred) be implemented as read. This motion was seconded and unanimously approved by the Committee.

CRITERIA DISCUSSIONS FOR PHASE I PDL DRUG CLASSES
The Committee reviewed the current criteria for drugs in PDL Phase I, which were identical to the previous version. A motion was made to maintain the existing criteria for year three of PDL Phase I drug classes. This motion was seconded and unanimously approved by the Committee.

CRITERIA DISCUSSION OF NEW DRUG CLASSES
The Committee reviewed the proposed new criteria for the six new PDL drug classes. A motion was made to accept the criteria as is written. This motion was seconded and unanimously approved by the Committee

CRITERIA DISCUSSIONS FOR NEW DRUG CLASSES

The Committee reviewed the criteria for new drugs in current Phase II and III PDL eligible classes. A motion was made to accept the criteria as is written. This motion was seconded and unanimously approved by the Committee.

The next meeting of the P&T Committee will be scheduled for early March 2006. The meeting was adjourned.